

**Remarks/Arguments:**

This response supplements the response filed February 18, 2009 to the Final Office Action issued on August 19, 2008. Applicants incorporate by reference their February 18, 2009 response.

Applicants herein have amended claim 1, 9, 12, and 25, canceled claim 10, and added new claims 28 and 29. Support for the amendments can be found, for example, in the first and second paragraphs on page 5, in the third paragraph on page 7, and in the second paragraph on page 12, bridging page 13. The amendments introduce no new matter.

**Information Disclosure Statement**

Applicants note that they submitted an Information Disclosure Statement (IDS) on November 5, 2007, but this IDS has not yet been considered by the Office. Applicants request consideration of this IDS.

**Interview Summary**

Applicants thank Examiners Hayes and Gembeh for the time and courtesy extended to Applicants' representative, Brian Cocca, during a telephone interview on April 28, 2009. Applicants' representative presented Applicants' position on the obviousness rejection of claims 1-6 and 8-14 as set forth in the August 19, 2008 Final Office Action.

Applicants submit the following remarks to complete the recordation of the interview.  
37 C.F.R. § 1.133; M.P.E.P. § 713.04.

Examiner Hayes raised the possibility that subparagraph "c" of claim 9 was indefinite, that the term "substantially free" as recited in claim 12 was indefinite, and that "functional bioequivalence" as recited in claim 10 was not enabled.

With respect to obviousness, Applicants' representative explained that propofol is highly lipophilic and nearly insoluble in water, and that these characteristics have necessitated solubilizing this drug with lipids or high concentrations of excipients. Applicant's representative further explained that U.S. Pat. No. 4,056,635 to Glen illustrates these problems with dissolving propofol because its propofol formulations require 10% Cremophor (a lipid), or a minimum 20% combination of a glycol and block copolymer.

No agreement was reached with respect to the rejected claims as a result of the interview. Applicants agreed to address the indefiniteness and enablement issues and submit additional arguments regarding the obviousness rejection in a supplemental response.

#### Indefiniteness and Enablement

Applicants disagree with the issues of alleged indefiniteness and enablement raised during the telephone interview, but have amended the claims identified by Examiner Hayes, and believe that the amendments obviate the issues.

#### Obviousness

In the August 18, 2009 Final Office Action, claims 1-6 and 8-14 were rejected as allegedly obvious over U.S. Pat. No. 4,056,635 (Glen) in view of U.S. Pat. No. 7,166,303 (Meadows). The Office Action relied on Example 10a of Glen for describing a propofol composition with 10% propylene glycol and 10% poloxamer 188, and reasoned that it would have been obvious for the skilled artisan to optimize these parameters to arrive at the claimed compositions. In addition, the Office Action cited to Meadows as describing aspects of the dependent claims not found in Glen. Applicants respectfully assert that the rejection fails to establish *prima facie* obvious because it does not provide a proper reason to modify and/or combine the cited references, and because it does not establish that aqueous propofol compositions having the claimed solubility and stability characteristics would have been predictable.

First, for the reasons given in the February 18, 2009 response, the Office Action has not given a proper reason to modify or combine the cited references because it has not shown that Glen or Meadows recognized the result-effectiveness of the claimed excipients or their combination, or that those of skill in the art would have considered it obvious to optimize Example 10a by lowering the amounts of poloxamer 188 and propylene glycol and maintaining the minimal lipids. Applicants add that Glen's Example 10a teaches 10% (by weight) of a glycol, whereas claims 1 and 25 recite 2% to 4% (w/v) polyethylene glycol, and submit that it would not be routine optimization to reduce the glycol concentration described by Glen 2.5- to 5-fold. Lacking a proper reason to modify or combine the references, the rejection fails to establish *prima facie* obviousness.

Second, the Office Action has not demonstrated that the skilled artisan could have predicted that its proposed modification of Glen would produce a composition clear to the naked eye and having the claimed stability. The claimed invention relates, in part, to the observed

synergy between poloxamer 188 and polyethylene glycol that allows high concentrations of propofol to be dissolved in an aqueous solution with minimal or no lipids, and with less than 15% (w/v) excipients. The claimed compositions are clear to the naked eye, and are more stable than conventional, lipid-based propofol emulsions as reflected in the clarity and stability descriptions and data presented in the specification (see, for example, pages 5 and 6, and Example 11 of the specification).

Applicants submit that based on the respective teachings of Glen and Meadows, and the recognition in the art that propofol is insoluble in aqueous solution, it would not have been predictable that a composition prepared by excluding lipids and including less than 15% excipients would be clear to the naked eye and would exhibit the claimed stability. Neither Glen nor Meadows provide any information about the clarity or stability of their respective formulations. Accordingly, the skilled artisan has no basis to predict whether propofol could remain dissolved in an aqueous solution comprising less than 1% lipids and less than 15% excipients, and whether such a composition would be stable over time.

Because the Office has not met its burden to provide a proper reason to modify and/or combine the cited references and to establish predictability of the claimed invention, the claimed compositions are not *prima facie* obvious, and the rejection should be withdrawn.

#### Double Patenting

Claims 1, 6, 8-12, and 25-26 were provisionally rejected for alleged obviousness-type double patenting over copending application 10/677,747. Applicants note that application 10/677,747 is abandoned, and request withdrawal of the rejection.

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Reply to Office Action of August 19, 2008

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Conclusion

Applicants request entry of the amendments submitted herewith, and reconsideration of the various rejections in view of the amendments and remarks. Applicants respectfully request a Notice of Allowance of all claims.

Respectfully submitted,



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